REMARKS

Reconsideration of the pending application is respectfully requested in view of the following remarks.

Status of the Application

Claims 1-54, 64, and 68-70 were previously submitted and are currently under examination. Claims 55-63 are amended to sharpen the claim language and provide a description of the subject matter which Applicants consider to be their invention. As amended, the claims are fully supported by the application as filed and no new matter has been added to the application by way of these amendments. Claims 65-67 were previously cancelled without prejudice.

Summary of the Office Action

Claims 1-64 and 68-70 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent 6,399,087 ("Zhang et. al.") in view of U.S. Patent 6,576,245 ("Lundgren et al.").

Discussion of the Claim Rejections

Claims 1-64 and 68-70 are rejected under 35 U.S.C. § 103(a). Applicants respectfully traverse the obviousness rejection.

Zhang discloses and teaches compositions containing propofol—without more. Indeed, the sole focus of Zhang is teaching the preparation of an optimized propofol formulation that is bacteriostatic or fungistatic. Zhang purportedly solves this problem by providing a formulation containing relatively low amounts of lecithin and soybean oil.

In contrast to the claimed invention, Zhang does not teach or suggest a container for its propofol compositions. Zhang, in fact, does not even mention a container or its equivalent. Because of this deficiency, Zhang, alone, cannot render any of the instant claims obvious.

The Office Action acknowledges this deficiency, but purports to cure it by the combination of Zhang and Lundgren. Office Action contends that Lundgren discloses low molecular weight peptide-based thrombin inhibitors in a primary package sealed with a rubber stopper or plunger containing bromobutyl rubber. The Office Action states that the

combination of the references is proper because "bromobutyl rubber would inherently work for a low molecular weight (1,000 M.W.) composition such as propofol (M.W. 178.28)." *See Office Action, p. 4.*

Applicants respectfully submit that Lundgren is not analogous art to Zhang. Lundgren it is directed to solving the problem of degradation of certain peptide-based thrombin inhibitors, purportedly by using a rubber stopper or plunger containing bromobutyl rubber (as opposed to chlorobutyl rubber). This is in marked contrast to Zhang which is directed not to solving the problem of peptide degradation, but to reducing microbial growth in propofol compositions. As the components (peptide-based thrombin inhibitors versus propofol compositions) and problems (degradation of specific peptide-based thrombin inhibitors versus microbial growth in propofol composition) facing Lundgren are not the same as that those facing Zhang, the ordinarily skilled artisan would not combine Zhang and Lundgren.

In addition, Applicants submit that the teaching attributable to Lundgren in the Office Action is not fairly based on the actual language of the reference. A fair reading of the reference by one skilled in the art is that Lundgren solves a problem associated with only those peptide-based thrombin inhibitors disclosed therein. Indeed, there is nothing in Lundgren that suggests that its solution is universally applicable to actives other than those specifically disclosed therein, let alone to the specific propofol compositions disclosed in Zhang. Indeed, there is no mention of propofol compositions in Lundgren at all.

Moreover, propofol is a very different compound from the peptides disclosed in Lundgren. While both propofol and Lundgren's peptides are smaller than 1,000 D, the peptides disclosed in Lundgren are much larger than propofol. Chemically, peptides are compounds containing two or more amino acids linked by the amide bond, while propofol is a small phenol derivative. Lundgren's peptides are water soluble, propofol is not water soluble. Peptides degrade by hydrolosis, while propofol degrades by oxidation. These features suggest that different containers may be optimal for the compounds disclosed by Zhang relative to those disclosed in Lundgren. Accordingly, those of ordinary skill would not look to containers appropriate for peptides as a means of storing propofol. The only basis for the combination is improper hindsight.

Even if one were to assume *arguendo* the asserted combination was proper, the combination would not provide the invention as claimed.

Lundgren teaches that bromobutyl rubber closures prevent degradation of peptide-based thrombin inhibitors, whereas chlorobutyl rubber closures do not. The Office Action inferred from Lundgren that "bromobutyl rubber would *inherently* work for a low molecular weight composition such as propofol" (emphasis added). In contrast, Example 33 of the instant application demonstrates a discovery by Applicants that not all bromobutyl rubber closures prevented degradation of propofol compositions. In fact, different types of bromobutyl rubbers (i.e., Rubbers 1, 2, and 3) had varying effects (52.9%, 93.4%, and 99.9% propofol percentage of control, respectively,) on propofol compositions containing 3% by weight soybean oil. In addition, whereas Lundgren discloses that chlorobutyl rubber closures did not prevent degradation of thrombin inhibitors, Example 33 shows that chlorobutyl rubber closures (Rubber 4) resulted in a 95.8% propofol concentration, that is, only a 4.2% loss of propofol compared to control. Thus, not only are the teachings of Lundgren inapplicable to propofol compositions (for the reasons set forth above), the asserted combination would not yield the invention as claimed.

Further, there is absolutely no recognition in either of the cited references that degradation or potency loss of a propofol composition could occur even if the weight percent of solvent used in such a composition was relatively low, or that the type of closure material would have an effect on the degradation or potency loss of such propofol compositions. For example, and as shown in Examples 32-37 of the instant application, propofol compositions containing relatively low amounts of solvent, e.g., less than 10% by weight of solvent (e.g., soybean oil), degraded to a greater extent when contacted with certain closure materials, whereas propofol compositions containing at least 10% by weight of solvent did not. As neither Zhang nor Lundgren recognizes the foregoing, neither motivates one skilled in the art to provide the invention as claimed, e.g., a sterile pharmaceutical composition of propofol in a container, comprising a container which includes a closure inert to propofol and a composition in the container, the composition in the container comprising propofol and less than about 10% by weight solvent for propofol (claim 1).

Additionally, claims 20, 23-27, 44, 47-51, 57, and 60-64 cannot be obvious over Zhang in view of Lundgren. Zhang does not disclose any containers for propofol compositions, nor does it teach any materials which are inert to propofol. Lundgren only discloses the benefit of stoppers containing bromobutyl instead of chlorobutyl in preventing degradation of low molecular weight thrombin inhibitors. Claims 25, 49, and 62 are directed to propofol compositions wherein the closure comprises a non-rubber or metal. Neither Zhang nor Lundgren disclose or even suggest the use of a non-rubber or metal closure for propofol compositions. Claims 26, 27, 50, 51, 63, and 64 are directed to propofol compositions wherein the closure is comprised of either chlorobutyl rubber coated with a flurorpolymer or a siliconized chlorobutyl. Lundgren actually teaches away from using a closure containing chlorobutyl by showing that chlorobutyl *increases* degradation of low molecular weight thrombin inhibitors over bromobutyl. Claims 23, 47 and 60 are directed to propofol compositions wherein the closure comprises bromobutyl coated with a fluoropolymer. Lundgren fails to disclose or suggest the use of a fluoropolymer in combination with bromobutyl. Finally, claims 20, 44, and 57 are directed to propofol compositions wherein the closure is comprised of material that is inert to propofol selected from a fluoropolymer, silicone, and mixtures thereof, and claims 24, 48, and 61 are directed to propofol compositions wherein the closure is comprised of siliconized bromobutyl. The sole discussion of siliconized bromobutyl in Lundgren occurs in Example 2 which is a comparison of low molecular weight thrombin inhibitors in a water solution of HPβCD versus a water solution of NaCl. Given the differences between low molecular weight thrombin inhibitors and propofol described above, there would have been no motivation or suggestion to utilize siliconized bromobutyl to prevent the degradation of pharmaceutical propofol compositions.

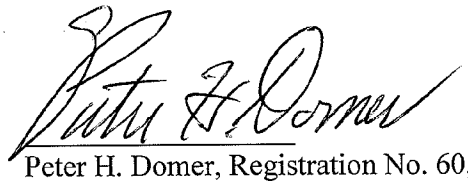
In summary, it would not have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the composition of Zhang with the teachings of Lundgren. Given the differences between peptides and propofols, one of ordinary skill in the art could not expect them to behave in similar fashions and would have no reasonable expectation of success even if one had combined references from non-analogous arts.

In view of the foregoing, Applicants respectfully request that the obviousness rejection be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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